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10/773,032	02/05/2004	Frank D. Lee	EPT-001C2	5991

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EXAMINER	
LIN, JERRY	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,032	LEE ET AL.	
	Examiner	Art Unit	
	Jerry Lin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,13,19-21,23,24,26-28,30-34,42 and 44-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,13,19-21,23,24,26-28,30-34,42 and 44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments and amendments, filed May 17, 2007, have been fully considered and they are deemed to be persuasive in part. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1-8, 13, 19-21, 23, 24, 26-28, 30-34, 42 and 44-47 are under examination.

Claims 9-12, 14-18, 22, 25, 29, 35-41, and 43 are cancelled.

Sequence Rules Compliance

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Such sequences are present throughout the drawings as well as throughout the specification. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because these sequences are not followed by a sequence identifier (SEQ ID NO:X). Applicants are given the same response time regarding this failure to comply as that set forth to respond to this office action. Applicants are reminded that it is required that SEQ ID Nos be amended into the specification at each sequence, and that when a

sequence is presented in a drawing regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. Failure to comply with these requirements may result in ABANDONMENT of the application under 37 CFR 1.821(g).

Drawings

3. The drawings are objected to because the drawing filed on November 13, 2003 are not legible. It is difficult to read the sequences on Figures 1 and 2 because the figures have a great deal of background noise. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If

the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

4. It is noted the color drawings were submitted on February 05, 2004. Color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Claim Rejections - 35 USC § 112, 1st Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 13, 19-21, 23, 24, 26-28, 42, and 44-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

peptide fragments bound to a capture agent with a site available for a secondary capture agent, does not reasonable provide enablement for peptide fragments with a separate site unavailable for a secondary capture agent upon binding of the first capture agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary – without a site for the secondary capture agent, one of ordinary skill in the art would have to develop a new type of secondary capture agent which would require a great deal of experimentation; (2) the amount of direction presented – the specification does not teach using any new types of secondary capture agents; (3) the presence or absence of working examples – there are no examples with new types of secondary capture agents; (4) the nature of the invention – the invention is directed to a combination of well-known techniques for detecting the presence and location of post-translational modification; (5) the state of the prior art – it is known in the prior art that a secondary capture agent requires a site to bind to for detection; (6) the relative skill of those in the art – the skill in the biological sciences is high; (7) the predictability or unpredictability of the art – the art is unpredictable; (8) the

breadth of the claims – the instant claims are drawn to peptide fragments of any size. Upon consideration of the Applicant's comments as well as considering the factors above, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The instant methods are drawn to a method of detecting and quantifying target proteins in a sample by fragmenting proteins in a sample, exposing the fragmented proteins to an addressable array of capture agents, wherein the capture agent binds to a PET that comprises the amino acid sequence encoded by the RNA comprising a splice junction and using a secondary capture agent labeled with a detectable moiety to detect a captured fragment.

In the Applicant's response on pages 12, the Applicants state that a "to create two antibodies to Katz's peptides, the artisan would likely be required to extend the length of Katz's peptides beyond Katz's preferred length of 5-12 amino acids." According to Applicants, the peptide fragment must be of a certain length in order to accommodate the binding of both the capture agent and a secondary capture agent. However, the instant claims make no mention of this requirement. Rather, the instant claims are generally drawn to a peptide fragment with a PET. As claimed, these peptide fragments would include those that are less than 12 amino acids in length. Furthermore, according to step 3 of claim 1, the entire PET is occupied by the capture agent and leaves nothing for the secondary capture agent to bind. Thus one of ordinary skill in the art would

have to conduct undue experimentation in order to create secondary capture agents that bind to small peptides.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-8, 13, 19-21, 23, 24, 26-28, 30-34, 42 and 44-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In step (2) of instant claim 1 recites "a peptide epitope tag of said target proteins" and "a peptide epitope tag (PET) unambiguously indicative." Since the limitations use a singular form and an indefinite article, it is unclear they are referring to the same PETs in step 1 or some other PETs.

In step (3) of instant claim 2 recites "said PETs." It is unclear to which set of PETs is the instant limitation referring.

Claim 1 recites the limitation "said captured polypeptide" in step 4. There is insufficient antecedent basis for this limitation in the claim. This limitation was not mentioned previously in the instant claims.

Instant claim 2 recites the limitation "the same target protein." Since the limitation uses a singular form it is unclear which of the target proteins in claim 1 is the limitation referring.

Claim 2 recites the limitation "the results" in line 4. There is insufficient antecedent basis for this limitation in the claim. This limitation was not mentioned previously in the instant claims.

Instant claim 4 recites the limitation "said capture agent" in line 1. Since the limitation uses a singular form, it is unclear which of the capture agents in claim 1 is the limitation referring.

Instant claim 5 recites the limitation "said polypeptide analyte" in line 2. Since the limitation uses a singular form, it is unclear which of the polypeptide analytes in claim 1 is the limitation referring.

Instant claims 6 and 47 recite the limitation "the same PET." Since the limitation uses a singular form, it is unclear which of the PETs in claim 1 is the limitation referring.

Instant claims 7 and 13 recite the limitation "said target protein." Since the limitation uses a singular form, it is unclear which of the target proteins in claim 1 is the limitation referring.

Claim 13 recites the limitation "the percentage". There is insufficient antecedent basis for this limitation in the claim. This limitation was not mentioned previously in the instant claims or in the in claims from which it depends.

Claim 13 recites the limitation "the total". There is insufficient antecedent basis for this limitation in the claim. This limitation was not mentioned previously in the instant claims or in the in claims from which it depends.

Instant claim 23 and 24 recites the limitation "said capture agent" in line 1. Since the limitation uses a singular form, it is unclear which of the capture agents in claim 1 is the limitation referring.

Claim 27 recites the limitation "the protein sources". There is insufficient antecedent basis for this limitation in the claim. This limitation was not mentioned previously in the instant claims or in the in claims from which it depends.

Instant claim 27 recites the term "said PET." Since the limitation uses a singular form, it is unclear to which set of PETs is the instant limitation referring.

Instant claim 34 recites the limitation "a said capture agent" in line 1. Since the limitation uses a singular form, it is unclear which of the capture agents in claim 30 is the limitation referring.

Claim 42 recites the limitation "said captured polypeptide" in step 4. There is insufficient antecedent basis for this limitation in the claim. This limitation was not mentioned previously in the instant claims.

Claim 45 recites the limitation "the results". There is insufficient antecedent basis for this limitation in the claim. This limitation was not mentioned previously in the instant claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to

> be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 3-5, 19, 24, 26, 28, 30-34, 42, 44, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dours-Zimmermann et al. (The Journal of Biological Chemistry (1994) Volume 269, Number 52, pages 32992-32998) in view of Jemmerson (Proc. Natl. Acad. Sci. (1987) Volume 84, pages 9180-9184) in view of Arenkov et al. (Analytical Biochemistry (2000) Volume 278, pages 123-131).

The instant methods are drawn to a method of detecting and quantifying target proteins in a sample by fragmenting proteins in a sample, exposing the fragmented proteins to an addressable array of capture agents, wherein the capture agent binds to a PET that comprises the amino acid sequence encoded

by the RNA comprising a splice junction and using a secondary capture agent labeled with a detectable moiety to detect a captured fragment.

It is noted that while applicants have amended the instant claims to state that the polypeptide analytes "comprises an amino acid sequence encoded by the RNA comprising a splice junction," this limitation only states that the polypeptide analytes contain some part of the amino acid sequence encoded by the RNA comprising a splice junction. The limitation does not state that polypeptide analytes necessarily include the amino acid sequence encoded by the RNA at the splice junction.

Regarding claims 1, 30, and 42, Dours-Zimmermann et al. teach a method of fragmenting proteins using a predetermined proteolytic protocol (page 32993, left column bottom) wherein the protein fragments contain epitopes that unambiguously indicative of the presence of a sample of the target proteins and comprise the amino acid sequence encoded by the RNA with a splice junction (page 32995); creating antibodies (capture agents) that selectively interact with the epitopes (page 32995) and contacting the antibodies to the protein fragments (page 32995) to detect the presence or absence of the target proteins (page 32995).

However, Dours-Zimmermann et al. do not teach wherein the proteins are denatured.

Regarding claims 1, 30, and 42, Jemmerson teaches developing antibodies specific for denatured peptide fragments (page 9181, left column; page 9182, right column).

However, neither Dours-Zimmermann nor Jemmerson teach presenting the antibodies (i.e., capture agents) in an array format.

Regarding claims 1, 30, and 42, Arenkov et al. teach presenting antibodies in an array format and using a secondary capture agent to detect the target protein (abstract; page 126, right column – page 127, left column, top).

Regarding claims 3-5, 24, 33, 34, and 46, Arenkov et al. teach wherein the capture agent is a antibody or a non-antibody (page 126); wherein the secondary capture agent labeled with a fluorophore binds to an epitope separate from the solvent accessible binding surfaces (abstract; page 126, right column – page 127, left column, top).

Regarding claim 26, Dours-Zimmermann teaches extracting the target proteins from whole cell lystate, which would include a billion molar excess of unrelated proteins or fragments relative to the target protein (page 32993, left column bottom).

Regarding claims 19 and 28, Dours-Zimmermann teaches wherein the cells are grown in an artificial environment (page 32993, left column, under "Cell Cultures"); and where the target protein may be a biomarker for a splice variant (abstract).

Regarding claims 31-32, Arenkov et al. teach wherein the solid support in disposed in a manner that encodes the identity of the capture agents (i.e., an addressable array) (abstract); wherein there are 2-100 or more different capture agents (abstract; page 125, left column bottom).

Regarding claim 44, Arenkov et al. teach wherein the array of capture agents interacts with different epitopes (page 126).

All the elements of the instant claimed method and instant claimed array are known in the references by Dours-Zimmermann et al., Jemmerson, and Arenkov et al. The only difference is the combination of these old elements into a single method or array. Thus, it would have been obvious to one of ordinary skill in the art to combine the methods of Dours-Zimmermann et al., Jemmerson, and Arenkov et al., because the method taught by each reference is not dependent on the other methods, and the combination of the methods may be performed to achieve predictable results of detecting the presence or absence of proteins encoded by splice variants.

10. Claims 2, 6-8, 13, 20-23, 26, 27, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dours-Zimmermann et al. (The Journal of Biological Chemistry (1994) Volume 269, Number 52, pages 32992-32998) in view of Jemmerson (Proc. Natl. Acad. Sci. (1987) Volume 84, pages 9180-9184) in view of Arenkov et al. (Analytical Biochemistry (2000) Volume 278, pages 123-131) as applied to claims 1, 3-5, 19, 24, 28, 30-34, 42, 44, and 46 above, and further in view of Wagner et al. (US 6,897,073 B2).

The instant methods are drawn to a method of detecting and quantifying target proteins in a sample by fragmenting proteins in a sample, exposing the fragmented proteins to an addressable array of capture agents, wherein the capture agent binds to a PET that comprises the amino acid sequence encoded

by the RNA comprising a splice junction and using a secondary capture agent labeled with a detectable moiety to detect a captured fragment.

Dours-Zimmermann et al., Jemmerson, and Arenkov et al. are applied as above.

However, neither Dours-Zimmermann et al., Jemmerson, nor Arenkov et al. does not teach determining the amount of target protein in the sample by averaging the results obtained from each said capture agent.

Regarding claims 2, 20, 21, and 45, Wagner et al. also teach a method of detecting proteins using arrays of protein-capture agents (abstract) which includes contacting the array with cleaved or denatured protein analytes (membrane bound proteins) from body fluids (column 35, lines 22-44) and quantifying the amount of a target protein by averaging the result (including if the total amount of the detected proteins is averaged by one spot in the array) (column 35, line 63-column 36, line 23; column 39, lines 12-50).

Regarding claims 6 and 47, Wagner et al. teach arrays with capture agents bind to the same PET (column 12, line 14 - column 13, line 30); furthermore, Wagner et al. teach finding proteins that bind to the same PET at different affinities (column 30, line 54 – column 34, line 45).

Regarding claims 7 and 8, Wagner et al. teach using cellular extracts which would contain multiple forms of protein such as pro-form or mature form proteins (column 35, lines 22-44).

Regarding claims 13, Wagner et al. teach detecting protein fragments (processed forms) of cellular extracts and determining the ratio of one form of protein to another form (column 45, lines 32-39; column 38, lines 43-65).

Regarding claim 23, Wagner et al. teach wherein a secondary capture agent may be used for detection using fluorescent methods (column 36, lines 24-57).

Regarding claim 27, Wagner et al. teach wherein the PET is identified based on a sequenced genome (column 30, lines 42-54).

All the elements of the instant claimed method and instant claimed array are known in the references by Dours-Zimmermann et al., Jemmerson, Arenkov et al., Wagner et al. The only difference is the combination of these old elements into a single method or array. Thus, it would have been obvious to one of ordinary skill in the art to combine the methods of Dours-Zimmermann et al., Jemmerson, Arenkov et al., and Wagner et al., because the method taught by each reference is not dependent on the other methods, and the combination of the methods may be performed to achieve predictable results of detecting the presence or absence of proteins encoded by splice variants.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerry Lin whose telephone number is (571) 272-2561. The examiner can normally be reached on 10:00-6:30, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JL/

/Shubo (Joe) Zhou/

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PRIMARY EXAMINER